PESTICIDE TESTING IN HUMANS: ETHICS AND PUBLIC POLICY

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Abstract

Pesticide manufacturers have increasingly tested pesticides in human volunteers over the past decade. The apparent goal of these human studies is to establish threshold levels for symptoms, termed No Observed Effect Levels. Data from these studies have been submitted to the United States Environmental Protection Agency (EPA) for consideration in standard setting. No ethical guidelines have been developed for studies of pesticides in humans, no governmental oversight is exercised, and no procedures have been put in place for the protection of human subjects.

To examine ethical and policy issues involved in the testing of pesticides in humans and the use of human data in standard setting, the Center for Children's Health and the Environment of the Mount Sinai School of Medicine convened an expert workshop in February, 2002 of ethicists, physicians, toxicologists and policy analysts. Following a peer consensus process the authors concluded that:

- EPA must establish ethical standards for all research it conducts, sponsors or accepts in pesticide registration or standard setting;
- EPA must actively monitor all such testing and enforce ethical standards;
- No study which violates ethical standards can be accepted in support of pesticide registration or standard setting;
- It is inherently unethical to use human studies to establish threshold levels for symptoms, and therefore, data from studies on humans must not be used by EPA in setting standards;
- All participants in human studies must be provided sufficient information in a form understandable within their own language and culture to enable them to provide fully informed consent;
- Any study that is scientifically invalid or that fails to include a sufficient number of subjects to provide statistically valid answers to the questions under investigation is inherently unethical and must not be considered in standard setting;
- It is not acceptable to conduct a study in developing nations when the risks and harms involved in the study would be considered unacceptable in an industrially developed nation.

Authors also strongly encouraged active biomonitoring of every pesticide currently in use to track human exposure, particularly in vulnerable populations, and to assess adverse effects on health.

Introduction

Pesticides are a diverse group of chemical compounds and include insecticides, fungicides, herbicides, and rodenticides. Pesticides have contributed to dramatic increases worldwide in crop yields. They have helped to limit the spread of disease. But pesticides also have harmful effects. Pesticides cause injury to human health as well as to the environment. The range of these adverse health effects includes acute and persistent injury to the nervous system, lung damage, injury to the reproductive organs, dysfunction of the immune and endocrine system, birth defects and cancer (1).

Since passage of the Food Quality Protection Act (FQPA) in 1996, chemical manufacturers have, with increasing frequency, assessed the toxicity of pesticides by testing them in human volunteers (2). The apparent purpose of these tests is to establish safe or threshold limits for human exposure, termed No Observable Effect Levels (NOELs). The manufacturers' stated rationale for the studies is to better understand the potential toxicity of pesticides. However, critics suggest that the apparent motivation is to reduce the number of safety factors that must be utilized in establishing pesticide standards.

The acceptance by EPA of human test results in standard setting raises ethical and policy concerns. These issues include the lack of ethical guidelines for research conducted by chemical manufacturers and submitted to EPA, the absence of procedures for minimizing harm to study participants and for subjecting them to no unreasonable risk, and the use of approaches for obtaining informed consent by subjects participating in these studies that may be less stringent than the approaches to informed consent that are required in the United States.

To consider these issues, the Center for Children's Health and the Environment of the Mount Sinai School of Medicine convened an expert workshop, *Pesticide Testing in Humans: Ethics and Public Policy*, on February 27, 2002 (*See below for a listing of the participants). In this paper we review the history of pesticide testing in humans, and we summarize the ethical and policy recommendations developed and supported by the authors.

Background

The history of federal regulation of pesticides over the past five decades reflects an increasing awareness of the adverse effects of pesticides on human health. It embodies the realization that pesticides can have harmful effects at levels previously thought to be safe, especially in vulnerable populations such as infants and children. Recognition of the inherent dangers of pesticides has led to the development of regulations intended to protect human health from pesticide exposure.

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) of 1947 is the primary federal statute governing the registration and use of pesticides. FIFRA requires the United States government to register all pesticides prior to their introduction in interstate commerce. Under FIFRA, no person may sell, distribute, or use a pesticide unless it is registered by EPA. In 1964, Congress passed an amendment to FIFRA which authorized the Secretary of Agriculture to refuse registration to pesticides that were unsafe or ineffective and to remove them from the market (3).

In 1970, Congress transferred the administration of FIFRA to the newly created EPA. This initiated a shift in federal policy toward greater emphasis on minimizing risks of pesticides to human health and the environment, and away from an older, economically based paradigm that focused principally on issues of pesticide efficacy in agricultural production (3). This new policy focus was expanded by passage of the Federal Environmental Pesticide Control Act of 1972 (FEPCA) which amended FIFRA by specifying methods and standards of control in greater detail.

In 1996, the Food Quality Protection Act (FQPA) was unanimously passed by the United States Congress and signed into law. FQPA amended FIFRA yet again, fundamentally changing the way in which EPA regulates pesticides (4). The law requires EPA to reassess over 9,000 current pesticide residue tolerances by 2006. The FQPA explicitly requires EPA to make the protection of human health the primary goal of pesticide regulation and to consider the special vulnerability of children and infants to the toxic effects of pesticides (5). EPA has been instructed in certain circumstances to apply a child-protective safety factor in setting pesticide standards to account for differences between adults and infants.

EPA Standard Setting Procedures

For many years the EPA has relied on studies conducted by private industry in formulating exposure standards for pesticides. Traditionally, pesticide standards have been based on toxicity assessments in rodent species. The goal of such testing is to define the toxicology profile of the pesticide and to establish symptom thresholds or NOELs (No Observed Effect Level), also known as NOAELs (No Observed Adverse Effect Levels) or LOAELS (Lowest Observed Adverse Effect Levels). A NOEL is defined as an exposure level at which there is no statistically or biologically significant increase in the frequency or severity of any effect between the exposed population and its appropriate control (6). Two ten-fold safety factors are then applied. First, the NOEL observed in rodents is divided by a factor of ten to account for the extrapolation from rodent to human. Then, that number is divided by a second factor of ten to account for variation among humans. Thus, the traditional practice had been to determine the NOEL in animals, divide that number by 100, and on that basis, calculate the pesticide standard, termed a "reference dose" or "tolerance" (2).

Following the passage into law of FQPA, pesticide manufacturers have been required, in certain instances, especially where developmental toxicity is suspected, to apply a third child-protective safety factor of up to ten-fold and thus to divide the NOEL obtained in animals by a factor of as much as 1,000 (10^3) in setting human standards. In response to this new requirement, some pesticide manufacturers appear to have undertaken testing in humans as a means of bypassing the need for the first ten-fold safety factor. Testing in humans may render unnecessary the safety factor that accounts for the extrapolation from animal to human. The net effect is that the NOEL determined in humans need be divided by a factor of only up to 100 to comply with the FQPA.

FQPA also requires EPA to consider the cumulative effects on human health that may result from multiple exposures to many pesticides (4). For example, both organophosphate and carbamate pesticides exert their toxic effects through the inhibition of cholinesterase. Therefore, risk assessment involving organophosphate pesticides must now involve consideration of the potential cumulative health effects of

the additional exposure to carbamate pesticides. This requirement has created an additional incentive for pesticide manufacturers to perform human testing to relax EPA pesticide tolerance thresholds.

Human Testing of Pesticides

Since the 1960's, chemical companies have submitted studies to EPA in which human research subjects were exposed to pesticides. In 1973 New York State prisoners were fed small amounts of the organophosphate pesticide chlorpyrifos and monitored for weeks to determine adverse effects at various exposure levels (7). A 1992 study, conducted on 38 men and 9 women at the Inveresk Clinical Laboratory in Scotland for the French chemical company Rhone-Poulenc had participants drink orange juice that contained either a placebo, or various doses of the carbamate insecticide aldicarb. Some participants experienced side effects including sweating, light-headedness, and headaches (2). A 1994 study at the University of California, Davis, funded by the Amvac Chemical Corporation involved 70 paid human volunteers. Participants were exposed to methyl isothiocyanate, the active ingredient in the soil fumigant metam sodium (8).

The pace of pesticide testing in humans appears to have accelerated in recent years. In the decade prior to the passage of FQPA in 1996, only a handful of human tests were submitted to the EPA. In the subsequent three years, the EPA received 14 new unsolicited human subject studies on 10 different pesticides (9). Two examples involve the organophosphate insecticides dichlorvos and chlorpyrifos.

Dichlorvos is classified by EPA as a "suggestive carcinogen", and "is a direct acting mutagen in *in vitro* mammalian test systems" (10). Additionally, "following a single oral dose to rats, dichlorvos was associated with a variety of neurological and physiological changes" (10). EPA reports that "there is a concern that dichlorvos may affect brain development, and that it may do so in ways not measured in standard developmental toxicity tests" (10). In 1997, Medeval Laboratories in Manchester, England, conducted three studies funded by Amvac, in which a small number of adult men in Britain were paid to ingest dichlorvos dissolved in corn oil (2).

In 1998, after signing a seven-page consent form, dozens of college-age Nebraskans were paid $450 to swallow a pill containing chlorpyrifos. Chlorpyrifos is the active ingredient in Raid roach spray,

manufactured by the Dow Chemical Corporation. The students learned about this study after reading school newspaper ads urging students to call 402-474-PAYS to "earn extra money" (11).

The English Patients

Publication of *The English Patients: Human Experiments and Public Policy* by the Environmental Working Group (EWG) in 1999 was a landmark event in raising concern about the ethical and policy issues surrounding human testing of pesticides. This report noted that federal health agencies such as the NIH and FDA have rules governing the ethics and scientific quality of studies submitted for research purposes--the so-called Common Rule, but that the EPA has no such guidelines. The report focused public attention on small-scale industry studies in human adults that were being used by the EPA to set pesticide safety levels for the entire population of the United States, children included (2).

The *English Patients* noted that a number of the human studies it examined had failed to meet the scientific standards of contemporary research. Some of the studies were based upon fewer than 15 participants, all of them adults. Thus they contained too few subjects to permit obtaining statistically valid answers to the questions under investigation, and they provided no information on developmental or pediatric toxicity. The report also noted that EPA does not require companies that conduct human experiments to follow any human subjects protection protocol (2). The *English Patients* concluded with three recommendations:

> "1. The EPA should conduct a review of past and current human experimentation in the context of environmental policy making.
>
> "2. EPA should impose an immediate moratorium on human experimentation, of the type conducted for dichlorvos, aldicarb, and other pesticides for purposes of pesticide registration until an ethical review has been completed.
>
> "3. After completing the comprehensive review, and prior to any relaxation of the moratorium on the use of human experiments for pesticide registration, EPA should promulgate and adopt policy guidelines and procedures for pesticide testing"(2).

Lastly, the EWG argued that the use of human test results derived solely in adults provides no data on developmental toxicity and thus fails to fulfill the intent of the extra ten-fold child-protective safety factor required by FQPA (2).

EPA Scientific Advisory Board and Scientific Advisory Panel

Responding to public and professional concern about the testing of pesticides in humans, in December 1998 the EPA convened a joint meeting of the Agency's Scientific Advisory Board (SAB) and Scientific Advisory Panel (SAP). To formulate ethical guidelines for pesticide testing in humans, the group convened a public meeting on December 10-11, 1998 and issued a draft report. Because aspects of that report diverged from the tenor of the meeting, certain members of the Committee refused to sign the report. After a yearlong stalemate, a second meeting was convened on November 30, 1999. The group issued its final report on September 11, 2000. This report included a minority statement dissenting from several key findings of the main report (12,13).

A unanimous finding of the Committee was that bad science is inherently unethical. The report stated "Bad science is always unethical; research protocols that are fundamentally flawed such as those with sample sizes inadequate to support reasonable inferences about the matter in question are unjustifiable". The committee found that the cases of pesticide testing on human subjects that it was able to examine all relied upon sample sizes far too small to yield statistically meaningful results. For these reasons, members of the committee raised no objections at the meeting to a proposal to disallow human testing as a means of establishing NOELs for pesticides. However, the final majority report diverged from the tenor of the meeting. It stated instead that "If it can be justified at all to expose human subjects intentionally to toxic substances, the threshold of justification for such an action should be very high"(12,13).

Addressing the risk of harm to research subjects, the report stated "…it is not enough to determine a risk/benefit ratio; it is important to consider the distribution of risks and benefits, and to insure that risks are not imposed on one population for the sake of benefits to be enjoyed by another". Additionally, the report stated "Any policy adopted by the agency should reflect the highest standards of respect for human subjects and should prohibit research protocols that override the interests of subjects in order to obtain useful data".

Ultimately, the committee could not agree unanimously as to whether there are circumstances under which pesticide testing on human subjects can be justified. Page 35 of the final report states "it agreed that, generally, human dosing experiments are not appropriate if the primary intent of the study is to determine or revise a NOEL or NOAEL so as to eliminate the interspecies uncertainty factor". However, this statement was not included in the Executive Summary or Major Recommendations (12,13).

The committee concluded that if the use of human subjects in pesticide testing can be justified, the basis for that justification cannot be to facilitate the interests of industry or of agriculture. Human testing, the committee held, could be justified only to better safeguard the public health. Various committee members expressed doubt about the EPA's ability to translate this concern into enforceable regulations, but all members agreed with the basic principle. While noting the lack of consensus, the final majority report suggested that pesticide testing on human subjects would be permissible if all such research were reviewed in advance by an Institutional Review Board (IRB) in accordance with the protections of Part 45CFR46 (the "Common Rule"), and subject to scrutiny by the EPA. Furthermore, the majority report recommended that such studies be well designed, refrain from exposing developing humans to neurotoxic chemicals, and provide information not available via animal studies, study of incidental exposures, or other sources (12,13).

Two committee members issued a Minority Report that dissented from the Majority Report in several areas. It expressed concern that the final report did not accurately reflect the earlier consensus of the panel members. The dissenters, both of them pediatricians, argued that the final draft of the report was a "distorted and diluted version of the public proceedings of the Subcommittee" and "if accepted, it will serve to increase the health risks of children from pesticide exposure". The minority report explained that during the December 1998 meeting most of the members had expressed strong doubts about both the ethics and scientific validity of exposing humans to organophosphate pesticides, but that the first drafts of the proceedings did not reflect this consensus. The minority report went on to state that the subsequent draft reports contain many misrepresentations of statements made by committee members, as recorded in the transcript of the proceedings (12,13).

The minority report stated that the final report minimizes the risks to humans from intentional experimental dosing, and de-emphasizes the issue that "no limited human study will provide information about safe levels of intake of pesticides by humans, especially children". The Minority Report also argued that the final report did not adequately address the need for large numbers of subjects to achieve sufficient statistical power to find a small effect, and that the overly small human studies done by pesticide manufacturers were scientifically invalid for this reason alone. It stated that to find a small effect, at least 2500 subjects in each group were necessary, and that with the sample sizes of 7 to 50 subjects used in industry studies, there was a 3% to 4% chance of finding an effect. The Minority Report concluded that the "there is strong documentation that the human studies done by the pesticide manufacturers were scientifically invalid" (12,13).

Recent Developments

During 1999, in response to mounting criticism from environmentalists and physicians, the Clinton administration directed the EPA to stop accepting information from pesticide industry studies conducted on humans. The decision preempted the report from the EPA SAB/SAP, which had for months been deadlocked in their deliberations (7).

In November 2001 the Bush administration reversed the decision of the Clinton administration, indicating that it would now accept data from human tests. The new policy, which has not been formally announced or acknowledged, appears to disregard the recommendations of the EPA SAB/SAP Joint Subcommittee on Data from Human Subjects (9).

During 2001, the EPA evaluated three trials in which human volunteers had been subjected to doses of pesticides hundreds of times greater than levels the EPA had deemed safe. In one study conducted in Lincoln, Nebraska by a subcontractor to the Dow chemical corporation, volunteers were paid up to $460 to ingest doses of chlorpyrifos in concentrations up to 300 times higher than the level the EPA considers safe. One female volunteer who received the highest dose reported numbness in her upper arms which company officials ruled "possibly" related to the pesticide. Cholinesterase levels in her blood fell by 28 percent, a level unlikely due to chance. Other female participants reported headaches, nausea, vomiting, and

intestinal cramps. Dow scientists concluded that the pesticide did not produce any symptoms since similar symptoms were also seen in volunteers given a placebo and there was no clear dose-response pattern (14).

On December 14, 2001, the EPA announced another moratorium on human tests after considering the results of testing that exposes humans to pesticides. On September 5, 2002, the EPA signed a contract with the National Academy of Sciences create an expert committee to examine ethical issues related to human testing of pesticides. A report is scheduled to be completed by the end of 2003.

Recently, Crop Life America, a pesticide manufacturers' trade group, filed suit against the EPA. The lawsuit seeks to compel the agency to accept data from pesticide testing on humans. Oral arguments are scheduled for March 17, 2003 in the United States Court of Appeals of the District of Columbia.

ETHICAL ISSUES

Improvements in the protection of human research subjects have often followed tragedies such as the Nazi experiments during World War II, the making public of the Tuskegee syphilis experiment in the 1970's, and the 1999 death of a research participant in a University of Pennsylvania trial (15). The Doctors' Trial at the end of the Second World War led to the establishment of the Nuremberg Code, the first clear source of guidance for the ethical conduct of clinical research (16,17,18). Other guidelines include the Declaration of Helsinki, the Belmont Report and International Ethical Guidelines for Biomedical Research Involving Human Subjects (19,20,21).

The Common Rule

To protect human subjects in federally funded research, 16 federal agencies, including EPA, signed on to the Common Rule in 1991 (2). The Belmont Report (named for the meeting site) provided the framework from which the Common Rule was adopted (20). The Common Rule applies to research conducted by federal institutions as well as non-federal institutions that receive federal funding. According to the Common Rule, all investigators who conduct studies that receive funding from any of the 16 federal agencies bound by the Common Rule must obtain informed consent from subjects (15). Additionally, the risks of participation must be reasonable "in relation to anticipated benefits, if any, to subjects, and the

importance of the knowledge that may reasonably be expected to result "(15). Any institution covered by the Common Rule must establish an Institutional Review Board (IRB) for oversight of human subjects research (22). Institutions that do not accept federal funding are not bound by the Common Rule, and therefore, are not required to establish IRB's to oversee their research. Perhaps one fourth of all clinical research conducted in the United States receives no federal oversight (11).

The Common Rule establishes informed consent as a critical part of the protection of human research subjects. This protection is necessary for ethical human research. However, recent work has suggested that, in fact, informed consent may not in some cases be a sufficient basis for ethical research with human subjects (23,24). Emmanuel, Wendler and Grady have raised questions about the adequacy of informed consent in assuring the protection of human research subjects and propose requirements that include, but go beyond informed consent, for the ethical conduct of human research (25).

Biomonitoring

Biomonitoring, the measurement of industrial chemicals in human tissues and fluids, has shown that all Americans carry a quantity of industrial chemicals or their metabolites in their blood, fat, mother's milk, semen, urine, and breath. This measurement is termed the "body burden" (26). In March 2001, the Centers for Disease Control and Prevention (CDC) presented its *National Report on Human Exposure to Environmental Chemicals*, the first of a planned series of annual studies of the types and amounts of industrial chemicals that American adults have in their blood and urine. One component of the report was the measurement of the levels of six urine metabolites from 28 organophosphate pesticides in a sample from the United States adult population. The study demonstrated that virtually all of the urine samples contained measurable amounts of all six organophosphate metabolites tested (27). Food is an important source of this exposure, and a recent study examining the presence of pesticides in food demonstrated that among some samples tested, almost 100 percent contained residues of as many as 14 different pesticides (28).

Biomonitoring studies have measured pesticide levels in the breast milk of nursing mothers in the United States (29) and have measured body burdens of organophosphate pesticides in American children (30). The existence of pesticide residues and their metabolites in human breast milk and in children is of

particular concern because children are more heavily exposed per kilogram of body weight and are more vulnerable than adults to the effects of pesticides (31). Infants and children have special characteristics (growth, development, and metabolism) that distinguish them from adults in their susceptibility to the toxic effects of pesticides. Children also possess behavioral traits which cause them to be exposed to higher doses of pesticides (31).

Public health scientists and practitioners use biomonitoring information for tracking, control and treatment. Biomonitoring data can also play a critical role in identifying novel hazards and high-risk populations, tracking trends in human exposure, and characterizing exposure levels that pose health hazards.

Many workshop participants suggested that biomonitoring provides important and useful information for risk assessment, particularly for determining patterns of exposure and the risks that pesticides pose to children's health. Workshop participants agreed that human biomonitoring should be conducted for every pesticide that is currently in use or present in the environment and posing human exposure risks. They also recommended that special consideration be given to assessing the body burdens of pesticides in children.

WORKSHOP RECOMMENDATIONS

The Need to Establish Ethical Guidelines for EPA Studies

The EPA has no formal, detailed guidelines or requirements at the present time for the ethical conduct of research submitted by private corporations for use in making regulatory decisions. This gap has the potential to give corporations that sponsor pesticide testing on humans freedom to produce data without adherence to established ethical standards for research. This lack of regulation and oversight is of great concern, particularly with regard to pesticide testing on humans. Hence, there is a pressing need to reverse the lack of oversight for pesticide research in humans and to create a level playing field by requiring that all studies submitted to the EPA for use in standard setting must be consistent with the Common Rule.

The authors agreed unanimously to the following recommendations:

Recommendation 1:

EPA must establish ethical guidelines for all research it conducts, sponsors, or accepts in registration applications.

Recommendation 2:

In its regulatory proceedings, the EPA must accept only research that is consistent with Common Rule requirements. No study that violates EPA ethical guidelines can be accepted in applications to the EPA.

Recommendation 3:

All research participants involved in studies that will be used in developing EPA exposure guidelines must be provided with adequate information for providing informed consent. To assure that participants are not subjected to undisclosed risks or harms, informed consent processes must be consistent with Common Rule requirements.

Recommendation 4:

EPA applicants and grantees must be held accountable for the ethical conduct of their research. Oversight and enforcement mechanisms must be developed and implemented by the EPA to ensure compliance with ethical guidelines.

Ethical Constraints on Research

The EPA has a fundamental responsibility to protect the environment and, thereby, to safeguard human health (32). In fulfilling its responsibility to commission sound research, EPA regulations must be designed to minimize the risk, magnitude, and duration of harm to humans. Accordingly, any study involving the administration of a pesticide to a human subject must be designed to minimize harm while subjecting the participant to no unreasonable risk.

Because of the possibility of adverse effects related to human participation in studies involving the administration of a pesticide, it is imperative that all such studies be supervised by a qualified physician. This physician must take direct responsibility for the well being of the subjects.

Recommendation 5:

Any study involving the administration of pesticides to humans must be supervised by a qualified physician. This physician must have direct responsibility for the well being of those participating in the

study. The physician must have the authority to intervene at any time to stop a study to minimize harm and risk of harm to subjects.

A core tenet of medical ethics is that studies should not knowingly do harm to humans, yet research involving deliberate human exposure to toxic chemicals appears to compromise this principle (33). By definition, all pesticide research designed to determine NOELs carries risk of unknown consequence. These potential risks include low-level health effects, some of which may be delayed in onset and follow the conclusion of the testing period. Historically, such effects have been recorded some time after some pesticide exposures that were thought to be safe, notably following low-dose exposure to some organophosphates, including certain pesticides (34).

NOEL studies inherently violate various ethical guidelines. Subjects are exposed to levels of pesticides that carry significant health risks. Also, there is no system in place to verify that NOEL studies conducted by chemical corporations are performed with the informed consent of the participants. Because the EPA does not require outside institutions to abide by any ethical protocol, the procedures of the chemical companies are not transparent. Additionally, the testing of pesticides in adults bears little relevance to pediatric toxicity.

Recommendation 6:

No results obtained from any NOEL studies in humans can be considered in the formulation of exposure guidelines by EPA.

The quality of scientific research is a fundamental component of the ethical conduct of science. It is agreed that bad science is inherently unethical.

Recommendation 7:

Any study that is not scientifically, e.g., does not include a sufficient number of subjects to provide statistically valid answers to the questions under investigation, is inherently unethical and must not be considered in standard setting.

To minimize harm to humans, and to avoid subjecting humans to unreasonable risks, it is necessary to begin studies by testing pesticides in animals. There are special considerations involved in the testing of pesticides in animals.

Recommendation 8:

Research on animals must precede research on humans.

Recommendation 9:

Animals must not be used in studies unless accurate and useful information can be obtained.

Given the current lack of knowledge about body burdens of pesticides in humans, children in particular, it is imperative that biomonitoring be carried out to determine the body burdens of pesticides in the general population.

Recommendation 10:

Human biomonitoring must be conducted for every pesticide that is currently in use or present in the environment and that poses human exposure risks. Special consideration must be paid to the body burdens of pesticides in children.

Human subjects research performed in countries outside of the United States for United States corporations or agencies is especially controversial (35,36). Guidelines must be enacted to prohibit the export to other nations of research deemed unacceptable in the United States. Of particular concern is the potential exploitation of subjects in studies carried out in developing nations.

Recommendation 11:

It is not acceptable to conduct a study involving humans in a developing nation when the risks and harms involved in the study would be considered unacceptable in an industrially developed nation. It is not acceptable to submit data from such studies in regulatory decision-making in the United States.

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